Chromatin structure and 3C-like data

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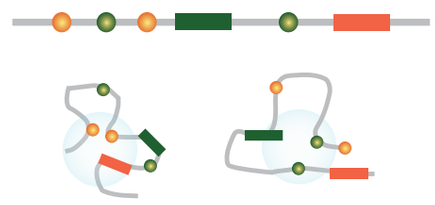
Structural Genomics Group (CRG)

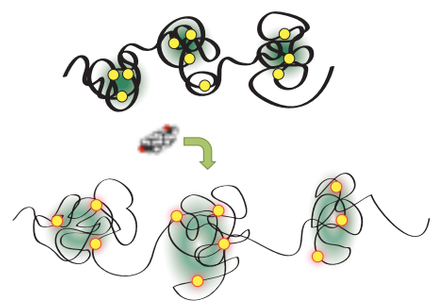
The role of chromatin structure

It can give insights into how distant genomic elements interacts with each other



It helps to understand the compartmentalization of chromosomes within the nucleus

It is essential to understand the mechanisms that regulate the cell



Chromatin definition

Chromatin is composed of DNA complexed with histones and other proteins

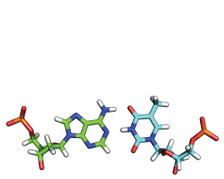
Chromatin formation enables the genome to be hierarchically packaged or condensed so that it can fit inside the nuclear space

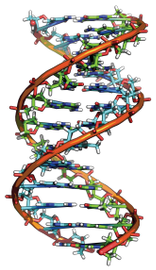
The compaction allows to modulate gene transcription, DNA repair, recombination, and replication

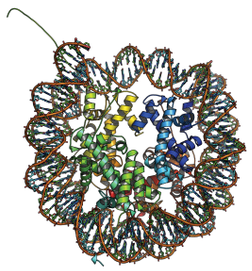
Chromatin structure is considered highly dynamic

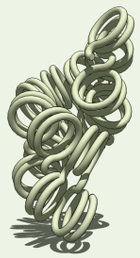
Resolution gap

Knowledge









IDM

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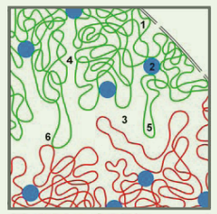
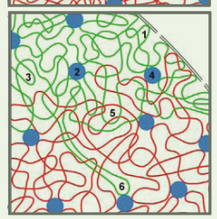
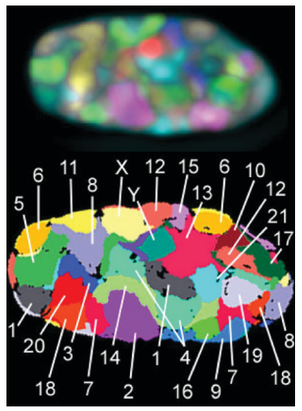






DNA length

10^{0} 10^{3} 10^{6} 10^{9} nt

Volume

10^{-9} 10^{-6} 10^{-3} 10^{0} 10^{3} μm^{3}

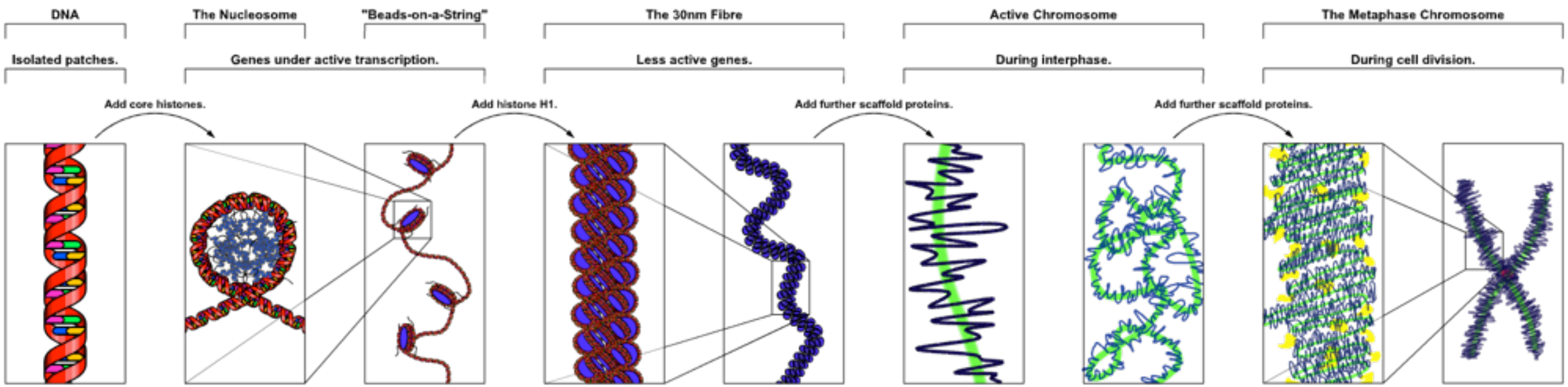
Time

10^{-10} 10^{-8} 10^{-6} 10^{-4} 10^{-2} 10^{0} 10^{2} 10^{3} s

Resolution

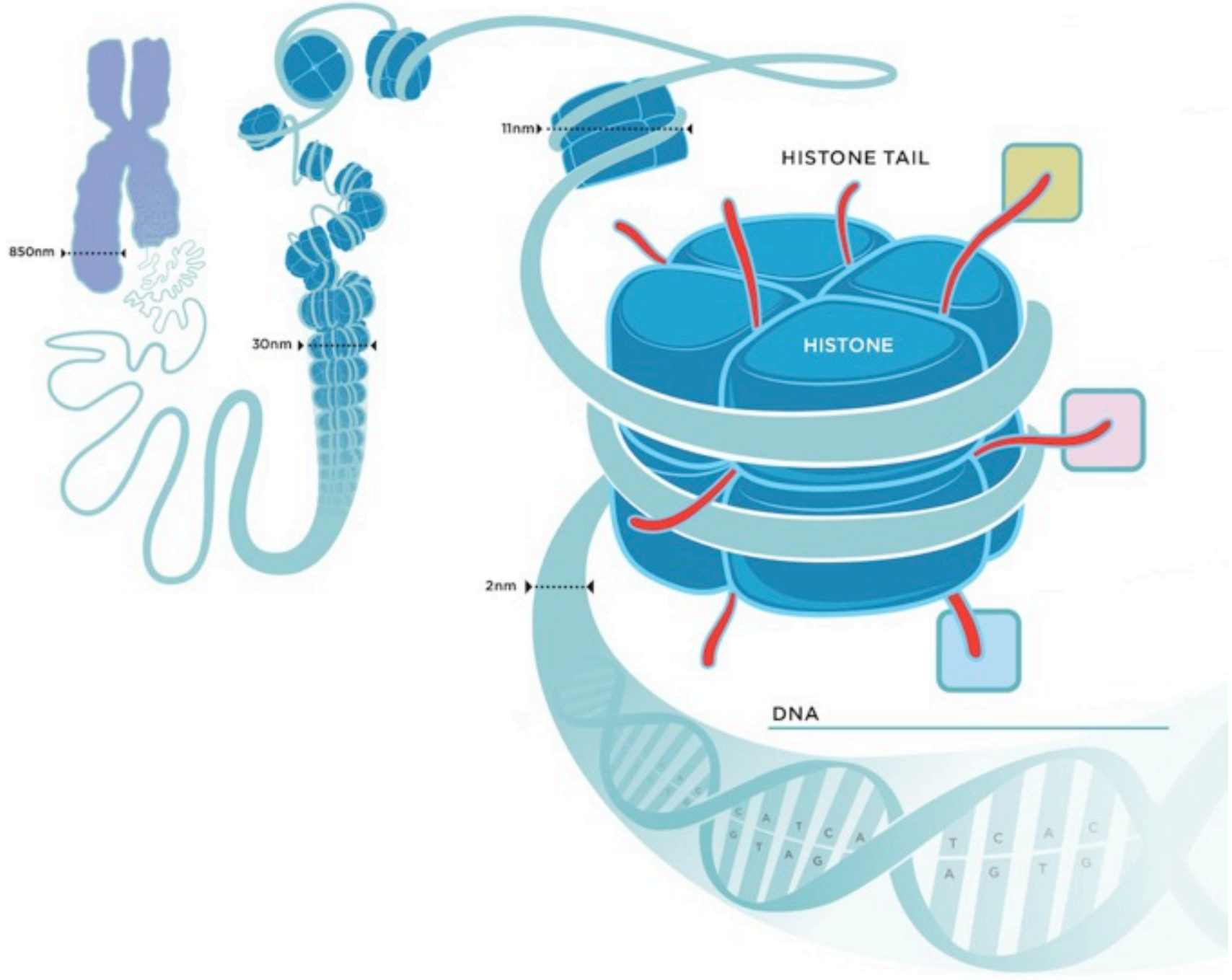
10^{-3} 10^{-2} 10^{-1} µ

Chromatin structures



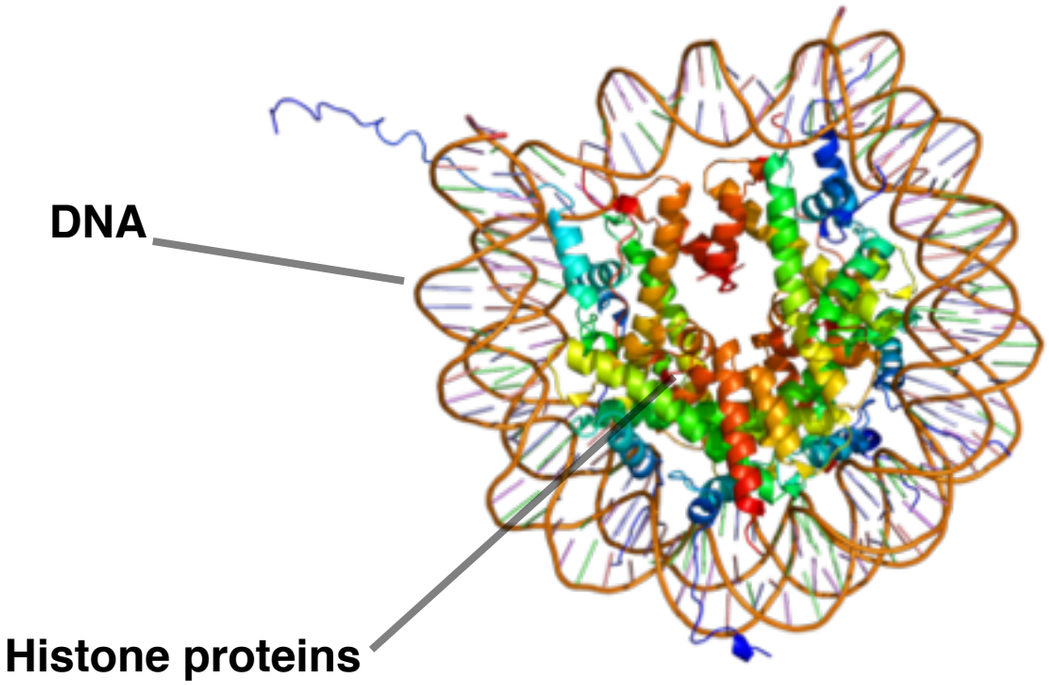
The nuclear organization of DNA

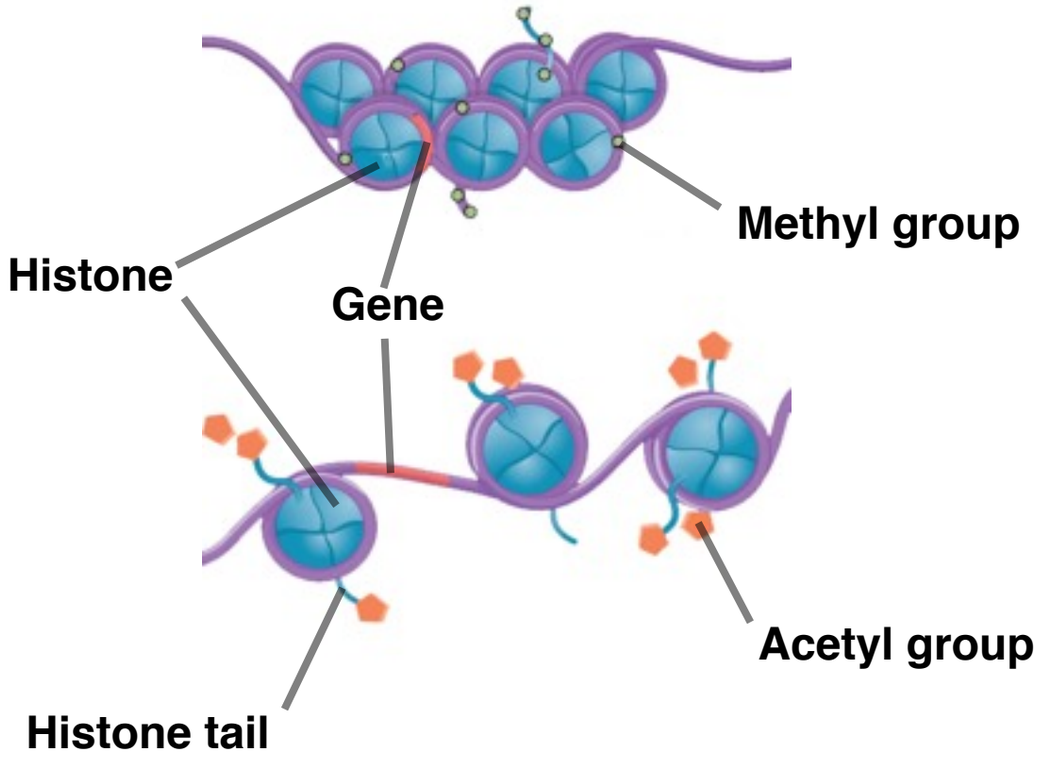
Chromosome **Chromatin fibre** **Nucleosome**

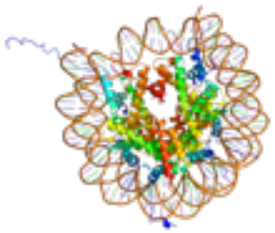


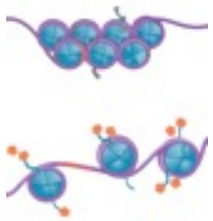
Adapted from Richard E. Ballermann, 2012

The nucleosome







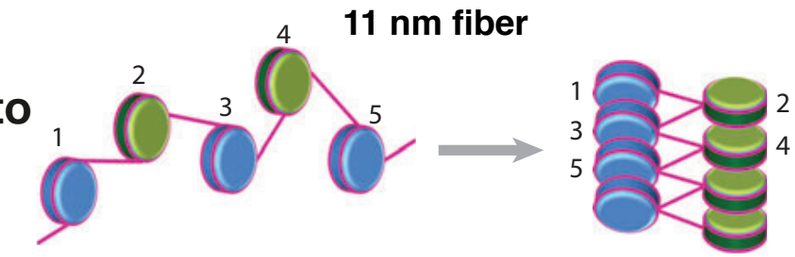


Histone modification effects

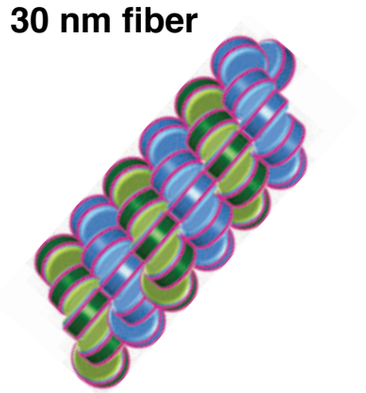
Type of modification	H3K4	H3K9	H3K14	H3K27	H3K79	H4K20	H2BK5
mono-methylation	activation	activation		activation	activation	activation	activation
di-methylation	activation	repression		repression	activation		
tri-methylation	activation	repression		repression	activation, repression		repression
acetylation		activation	activation				

The chromatin compaction levels

Several nucleosomes in a row form what is often referred to as a beads-on-a-string fiber (the 11 nm fiber)

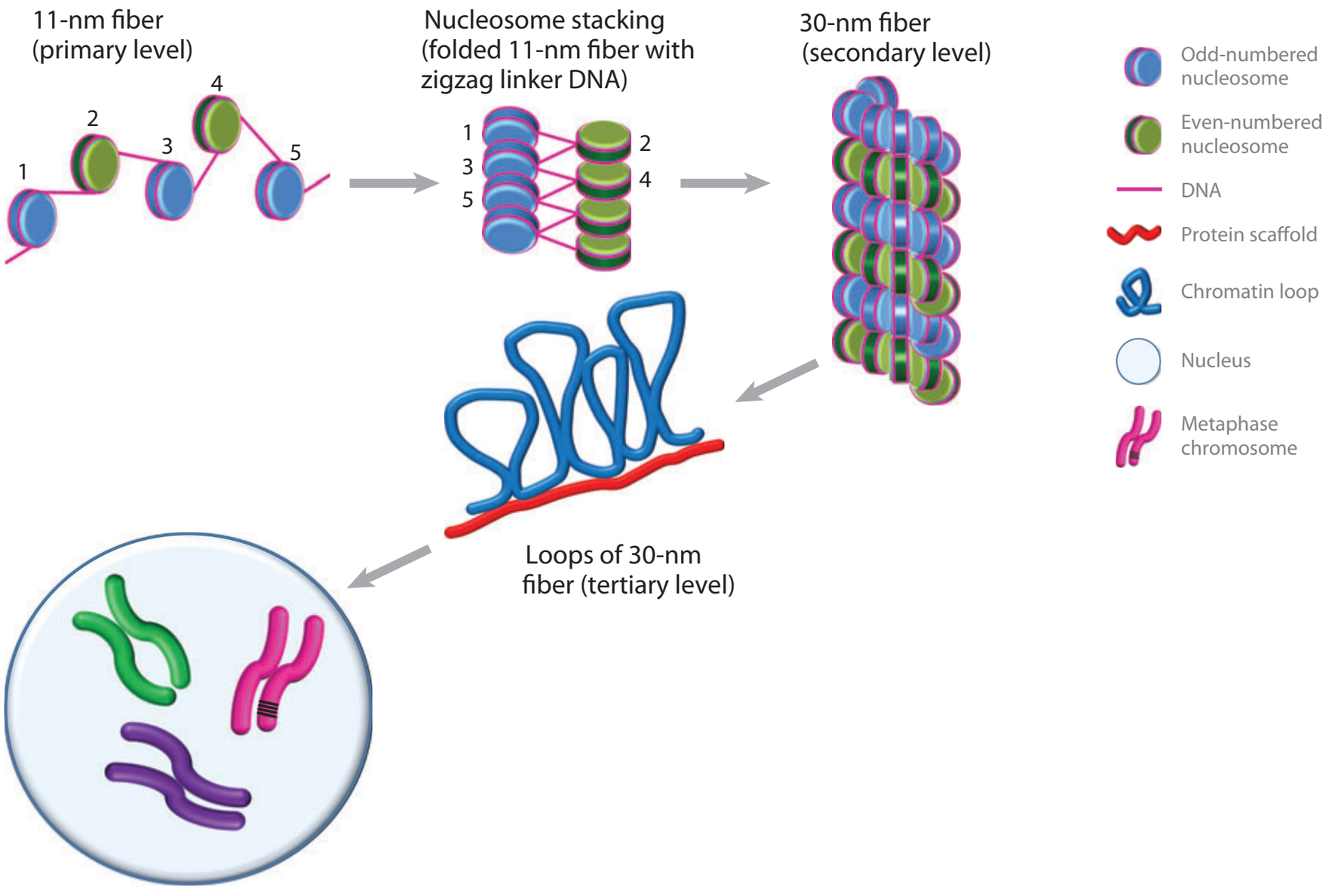


When histones H1 or H5, referred to as linker histones, are added to the 11-nm fiber, the condensed 30 nm fiber is formed



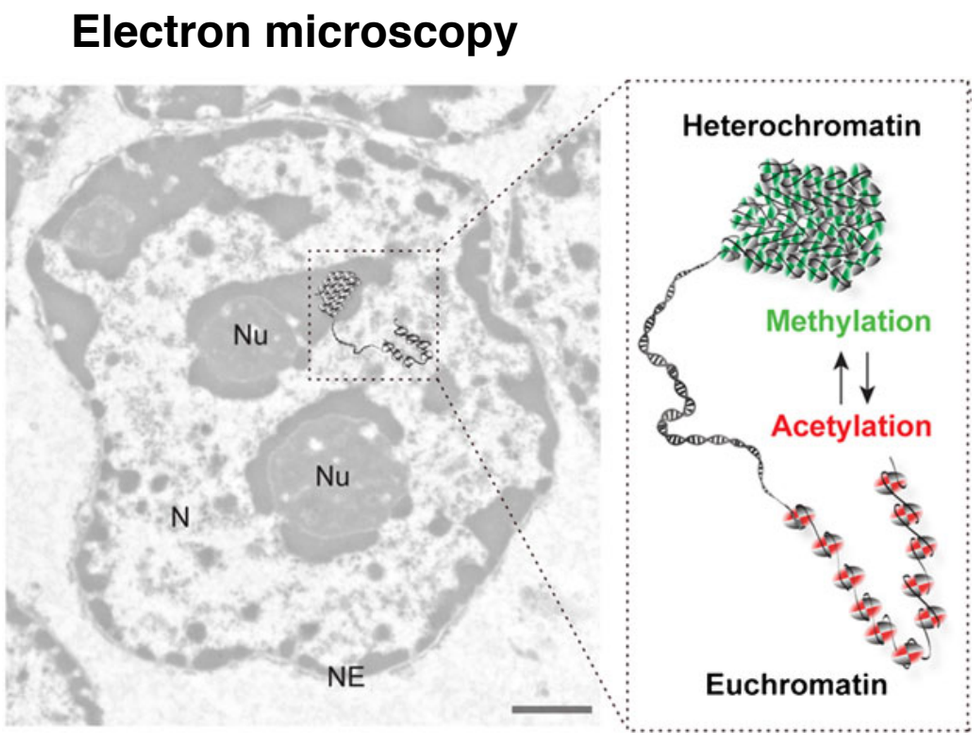
The 30 nm fibers form the next level of compaction by forming loops

The chromatin compaction levels



Adapted from Annu. Rev. Genomics Hum. Genet. 2012, 13:59-82

Euchromatin and heterochromatin

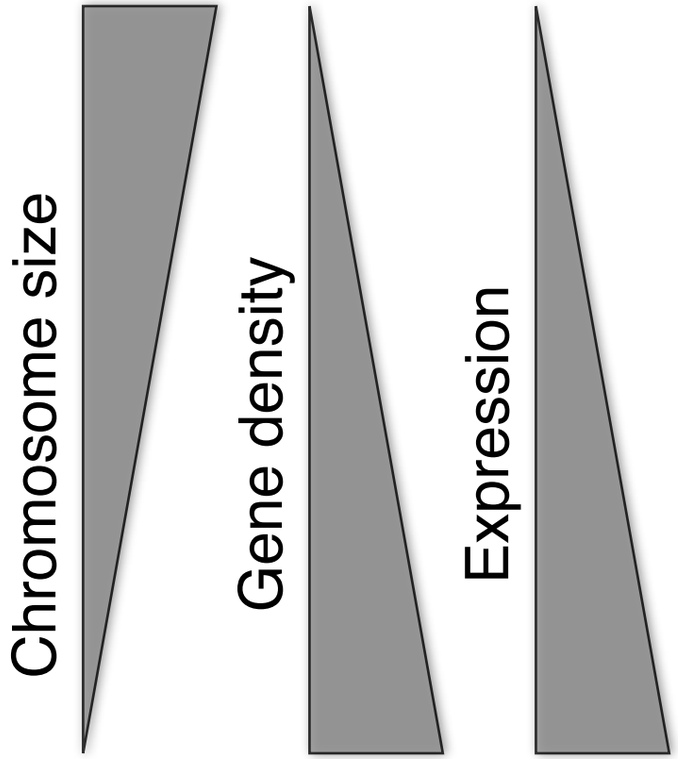


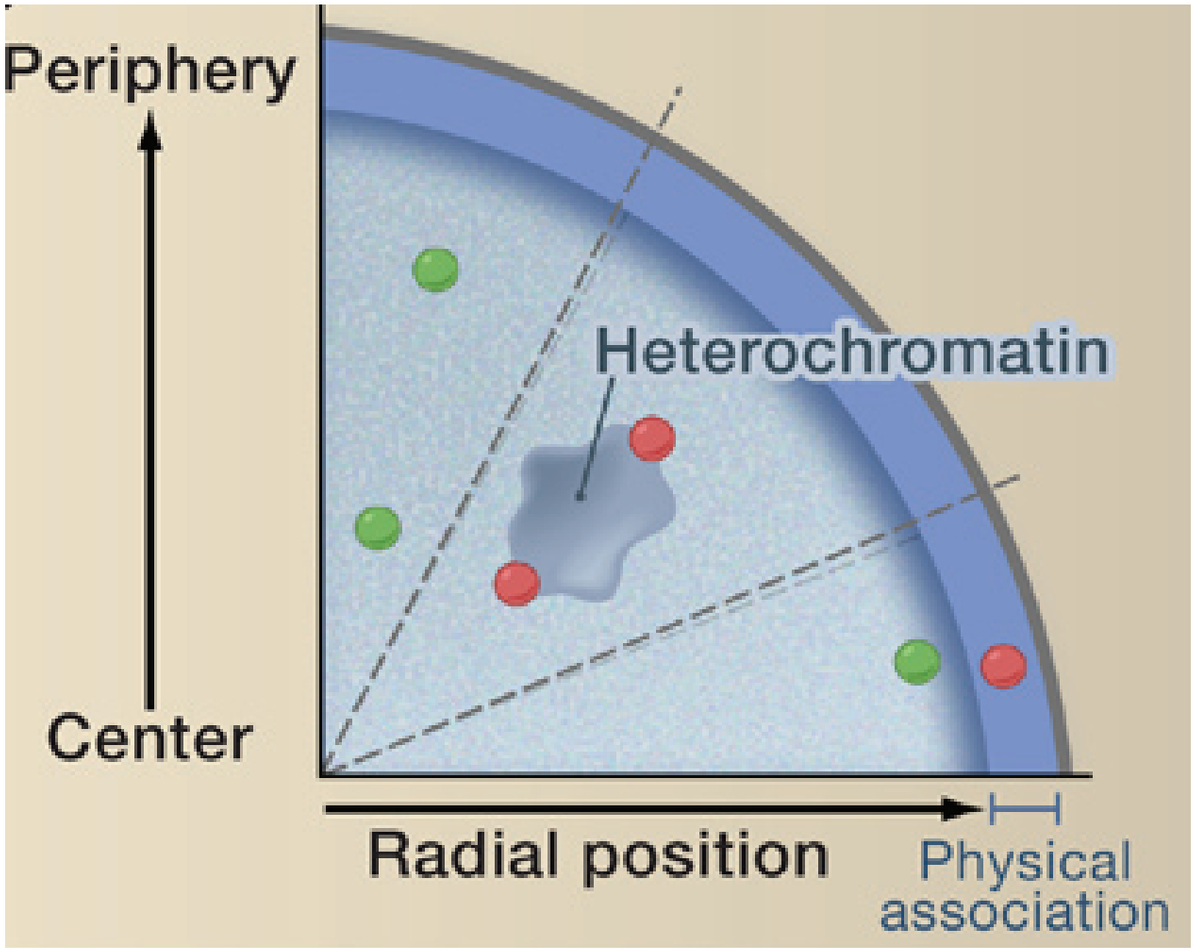
Euchromatin:
chromatin that is located away from the nuclear lamina, is generally less densely packed, and contains actively transcribed genes

Heterochromatin:
chromatin that is near the nuclear lamina, tightly condensed, and transcriptionally silent

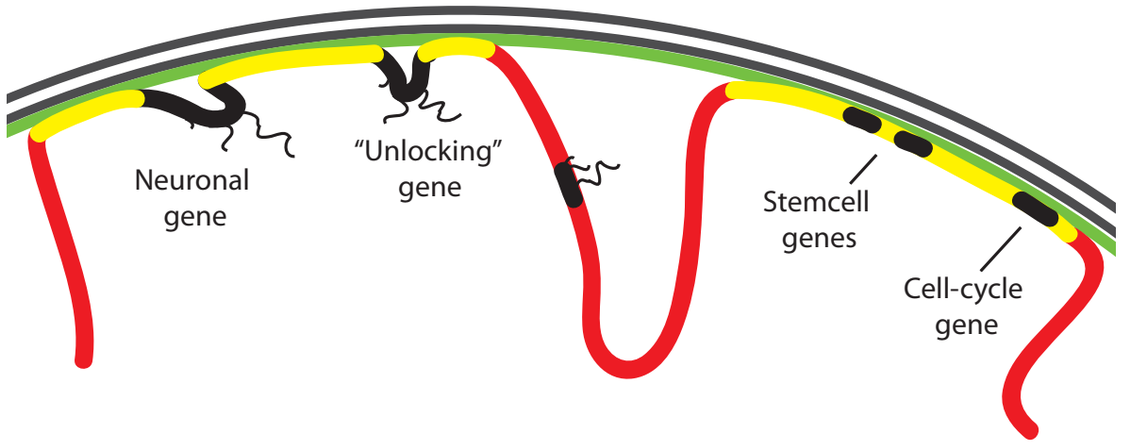
Complex genome organization

Takizawa, T., Meaburn, K. J. & Misteli, T. The meaning of gene positioning. Cell 135, 9–13 (2008).





Lamina-genome interactions

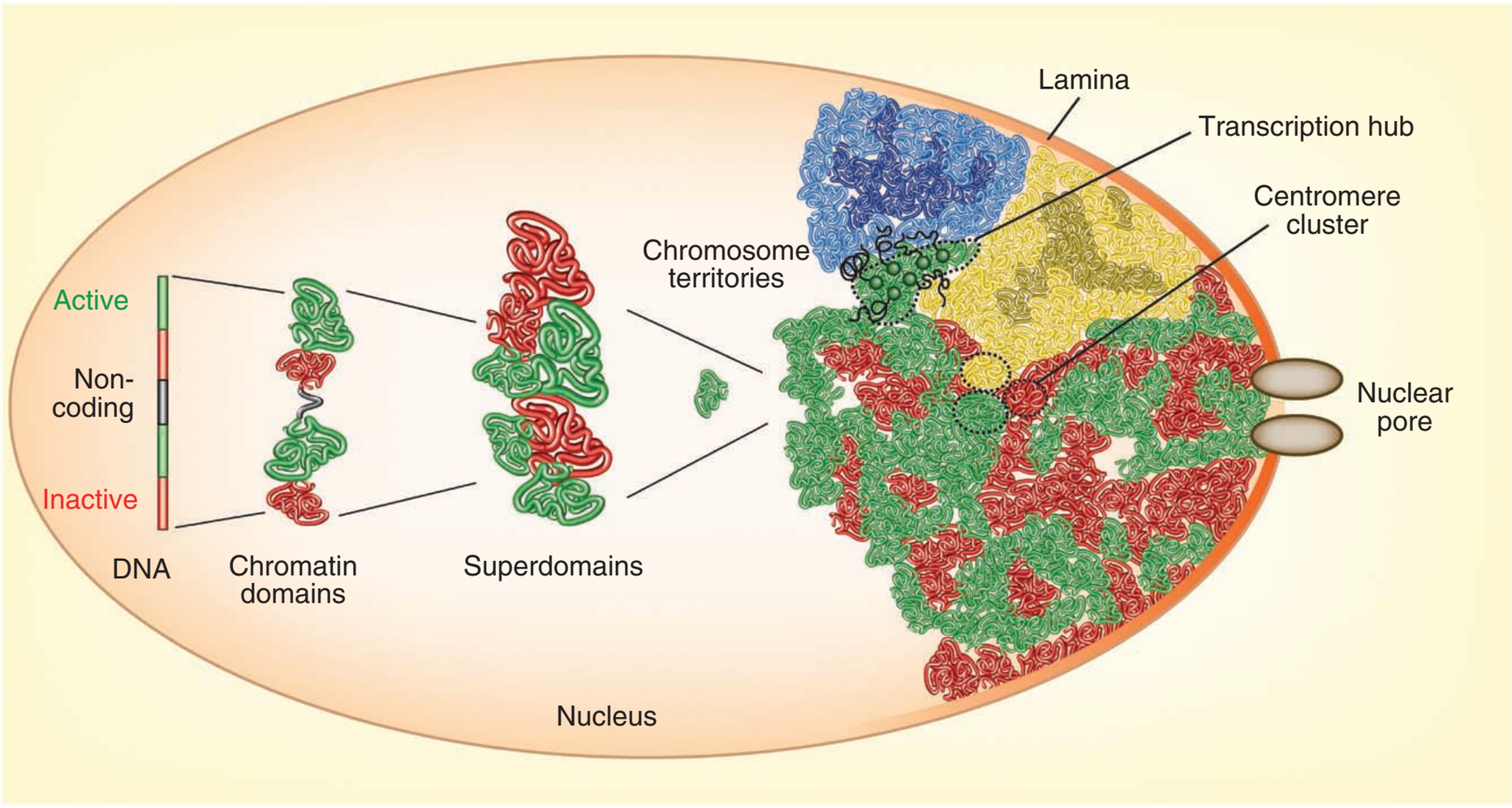


Most genes in Lamina Associated Domains are transcriptionally silent, suggesting that **lamina-genome interactions** are widely involved in the control of **gene expression**

Adapted from Molecular Cell 38, 603-613, 2010

Complex genome organization

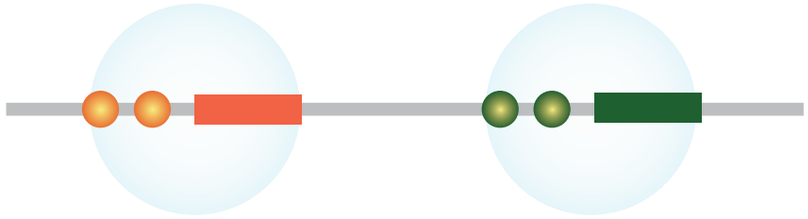
Cavalli, G. & Misteli, T. Functional implications of genome topology. Nat Struct Mol Biol 20, 290–299 (2013).



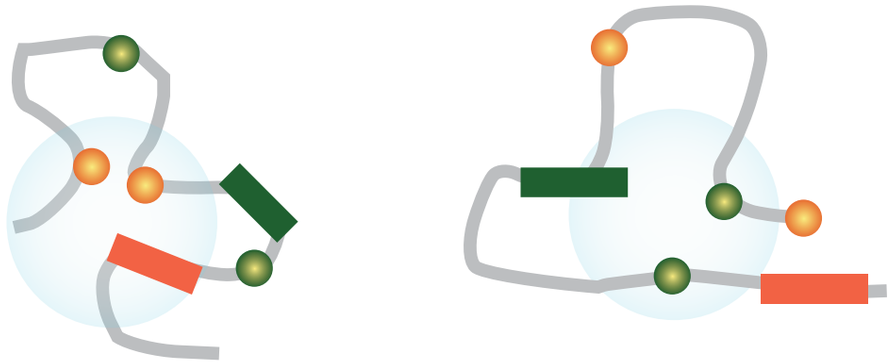
Marina Corral

Chromatin loops

Simple



Complex



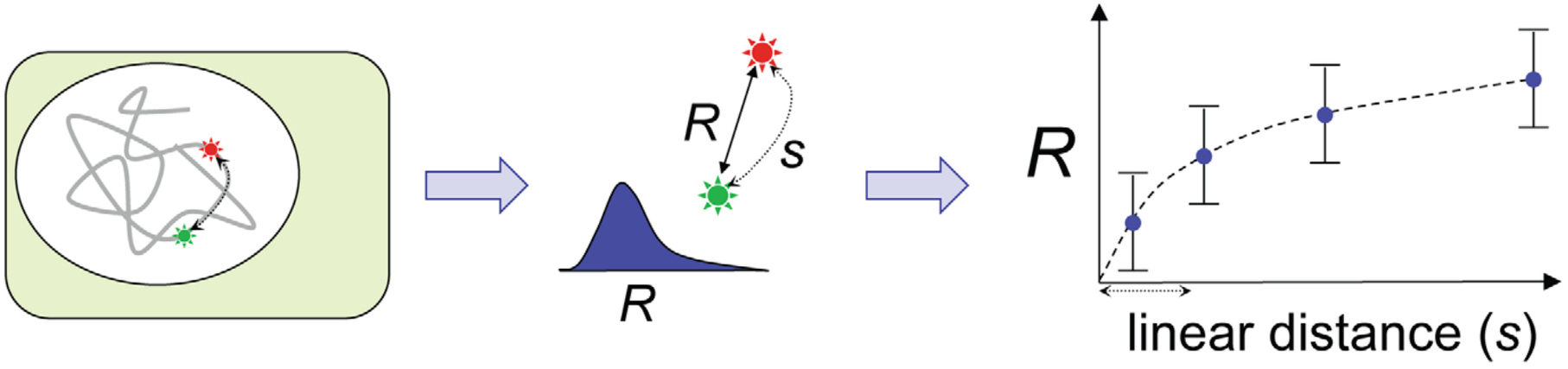
Loops bring distal genomic regions in close proximity to one another

This in turn can have profound effects on gene transcription

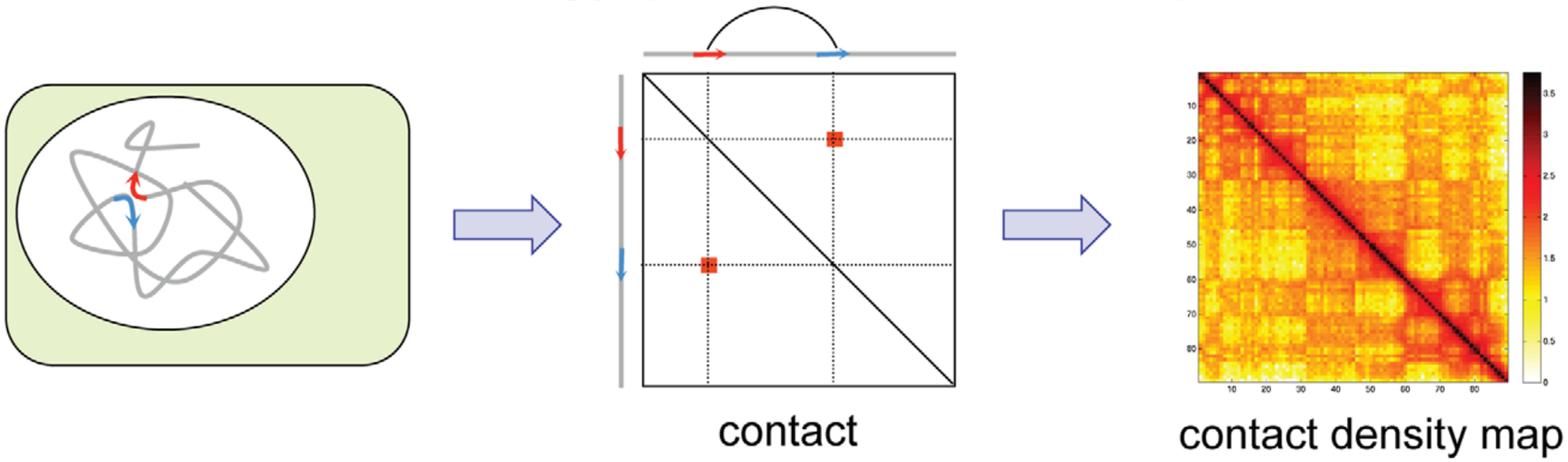
Enhancers can be thousands of kilobases away from their target genes in any direction (or even on a separate chromosome)

Main approaches

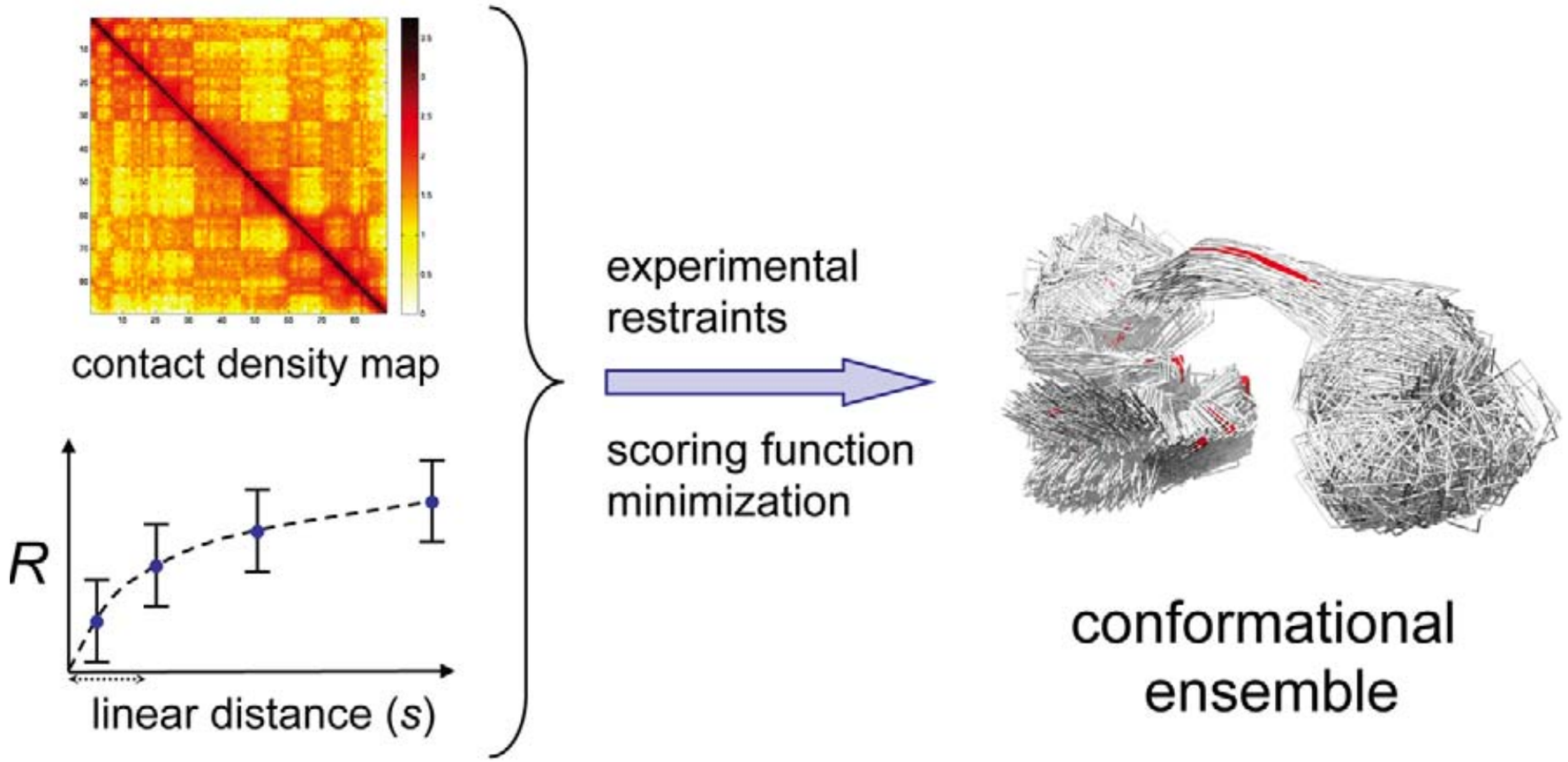
Light microscopy (FISH)



Cell/molecular biology (3C-based methods)



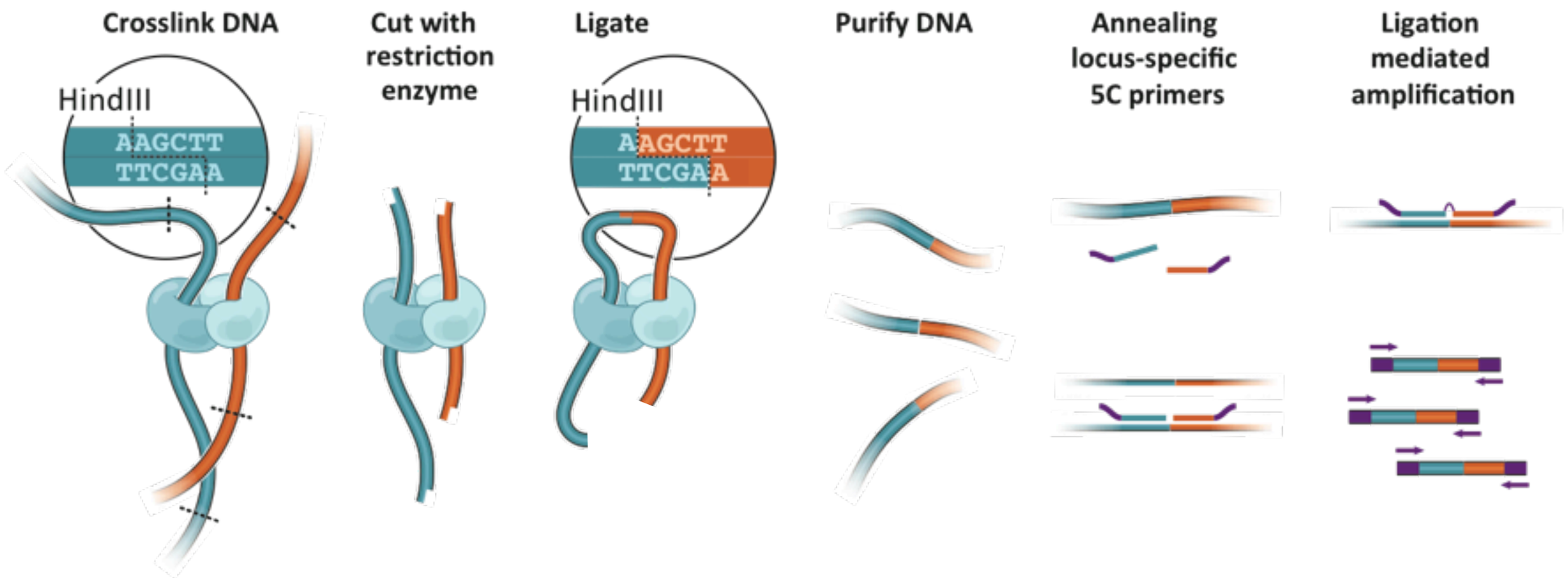
Restrain based modeling (IMP)



5C technology

http://my5C.umassmed.edu

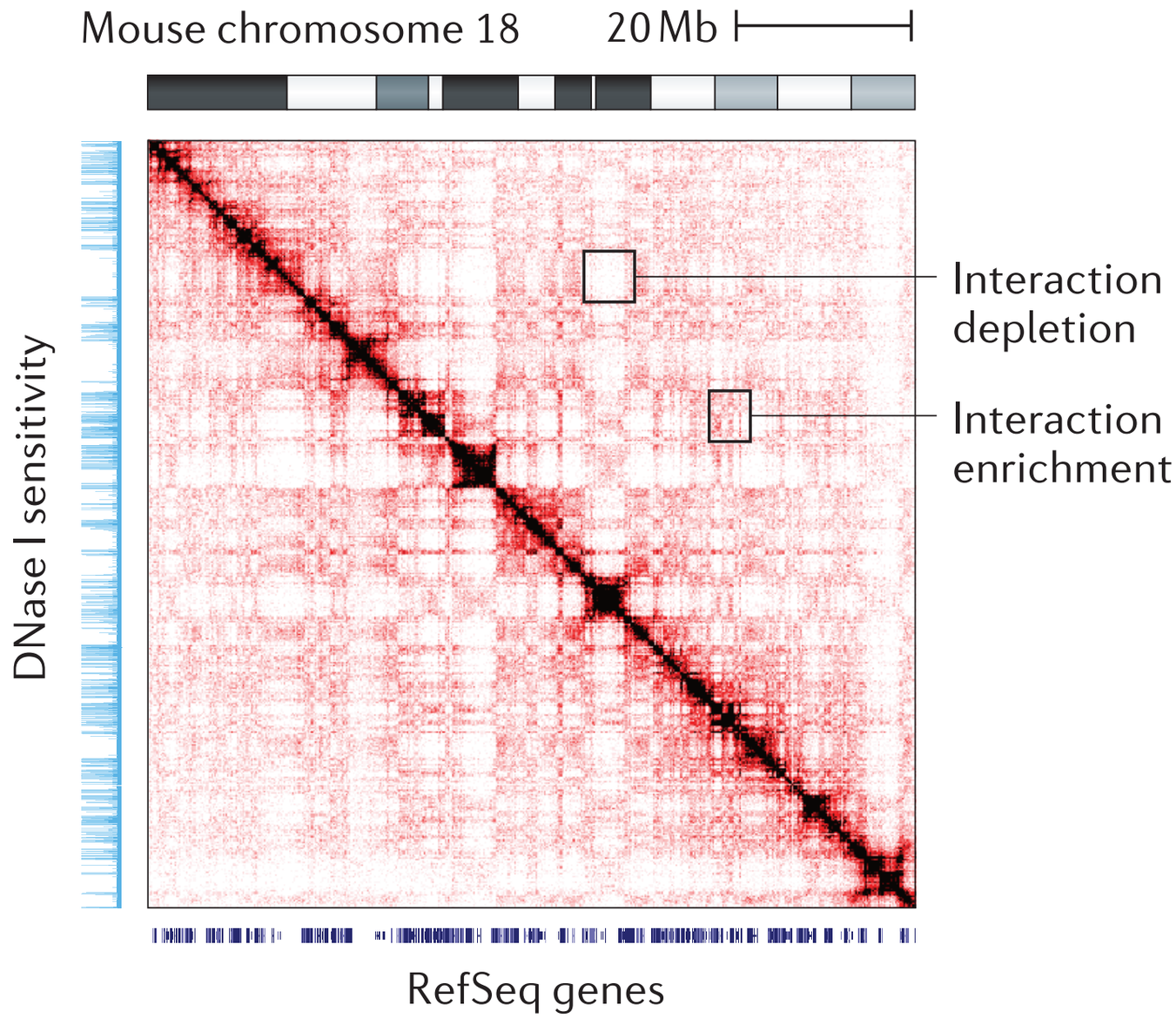
Job Dekker



Dostie et al. Genome Res (2006) vol. 16 (10) pp. 1299-309

Hi-C data and genomic tracks data

Dekker, J., Marti-Renom, M. A. & Mirny, L. A. Exploring the three-dimensional organization of genomes: interpreting chromatin interaction data. Nat Rev Genet 14, 390–403 (2013).



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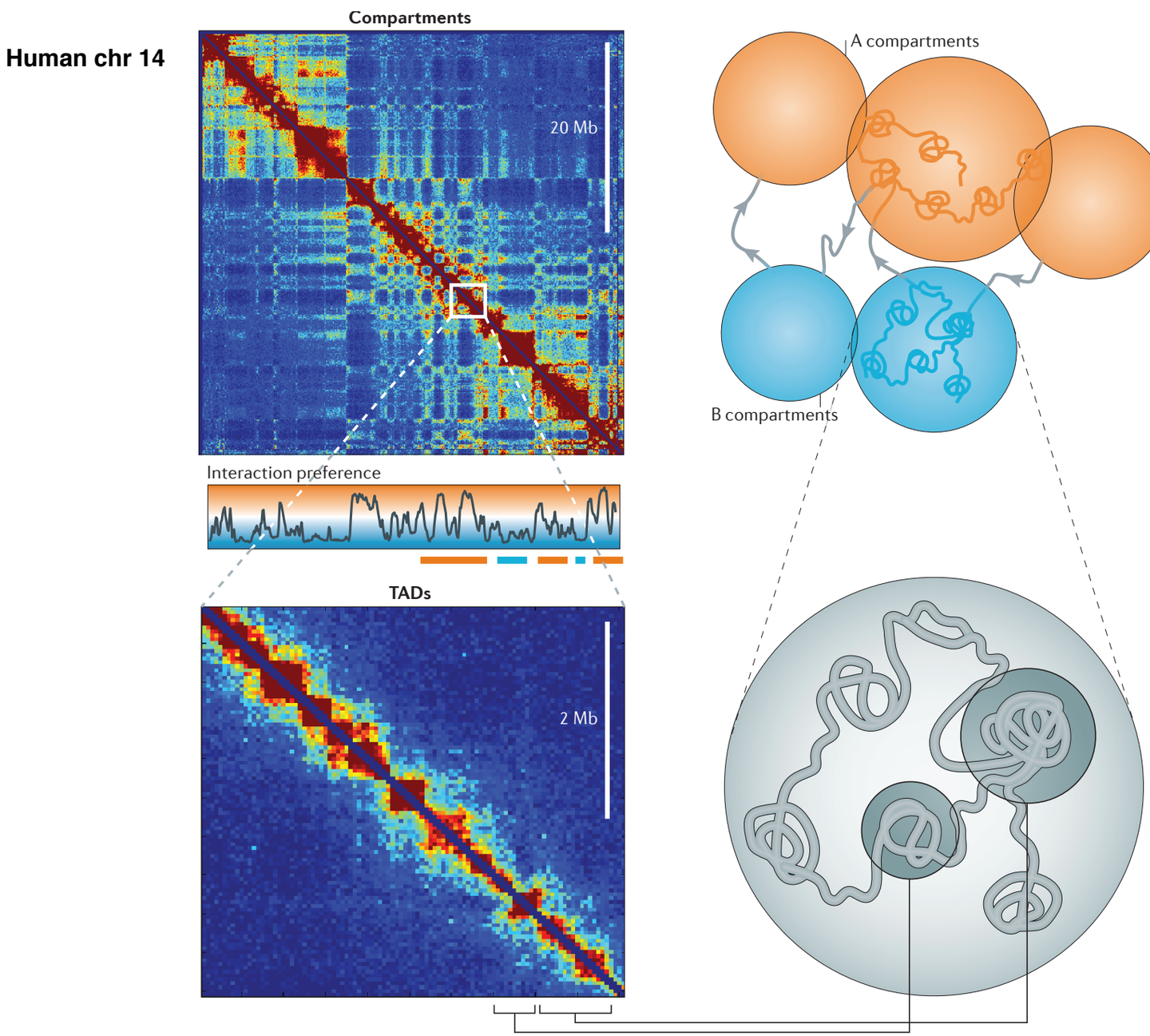
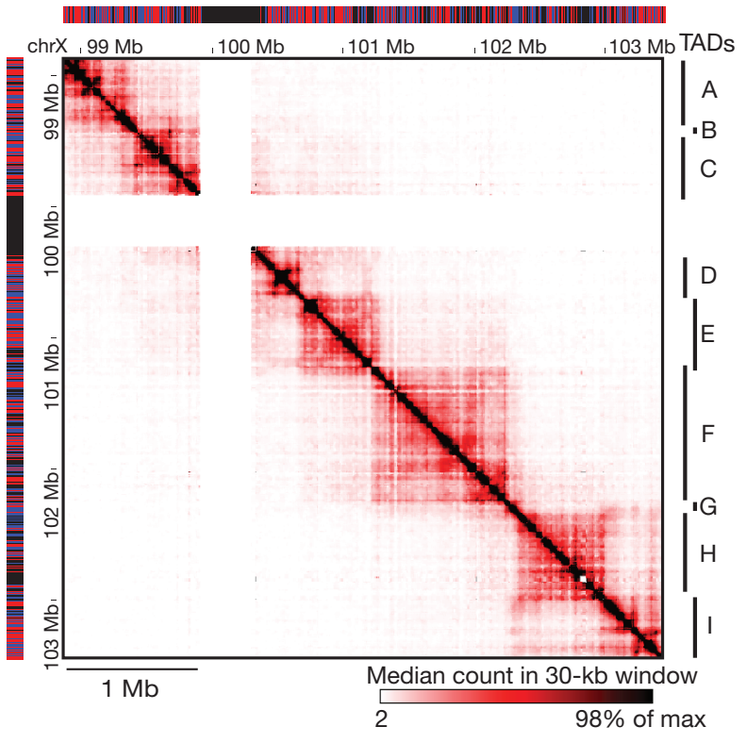
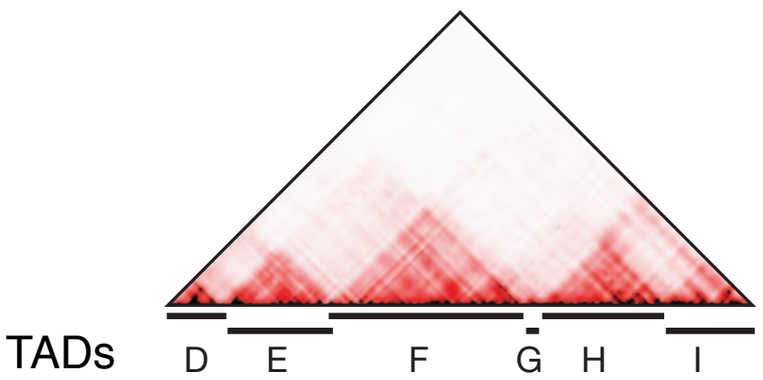
Dekker, J., Marti-Renom, M. A. & Mirny, L. A. Exploring the three-dimensional organization of genomes: interpreting chromatin interaction data. Nat Rev Genet 14, 390–403 (2013).



Topologically Associating Domains (TADs)





Topologically associating domains (TADs) can be made of up to hundreds of kb in size

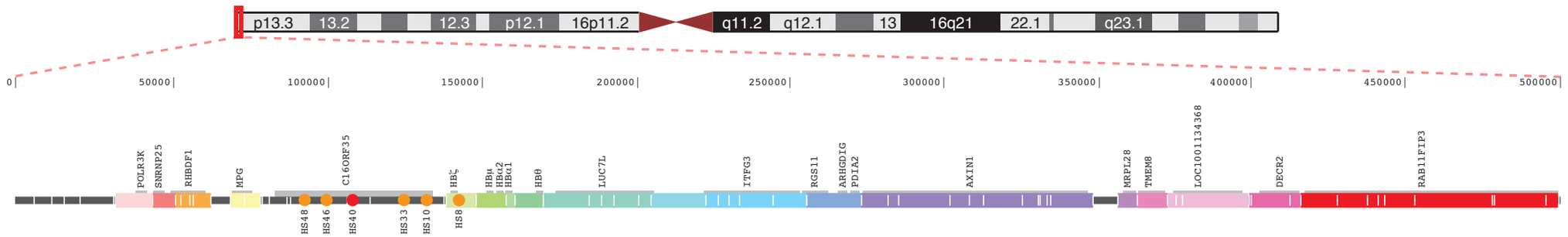
Loci located within TADs tend to interact more frequently with each other than with loci located outside their domain

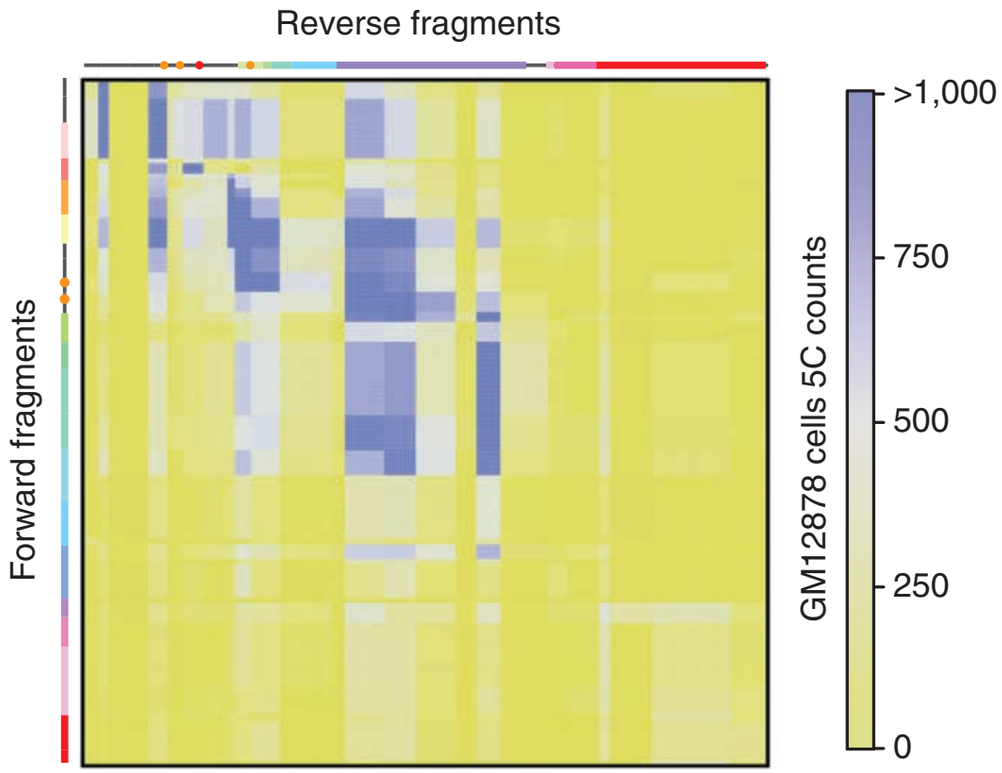
The human and mouse genomes are each composed of over 2,000 TADs, covering over 90% of the genome

Human α-globin domain

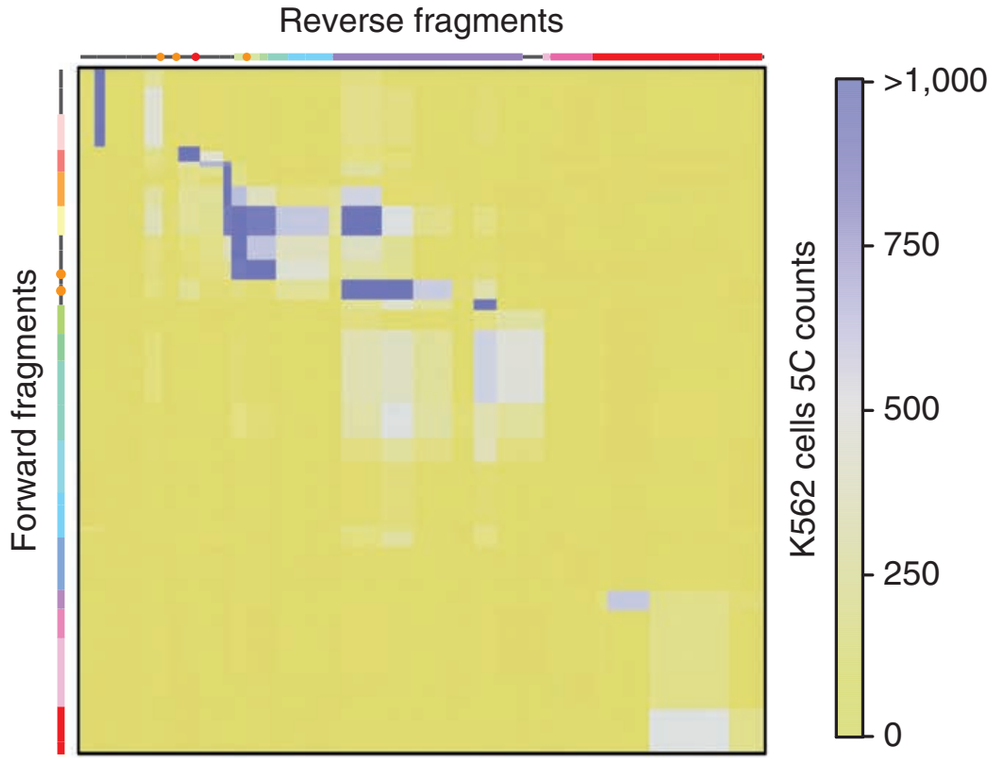
ENm008 genomic structure and environment

ENCODE Consortium. Nature (2007) vol. 447 (7146) pp. 799-816





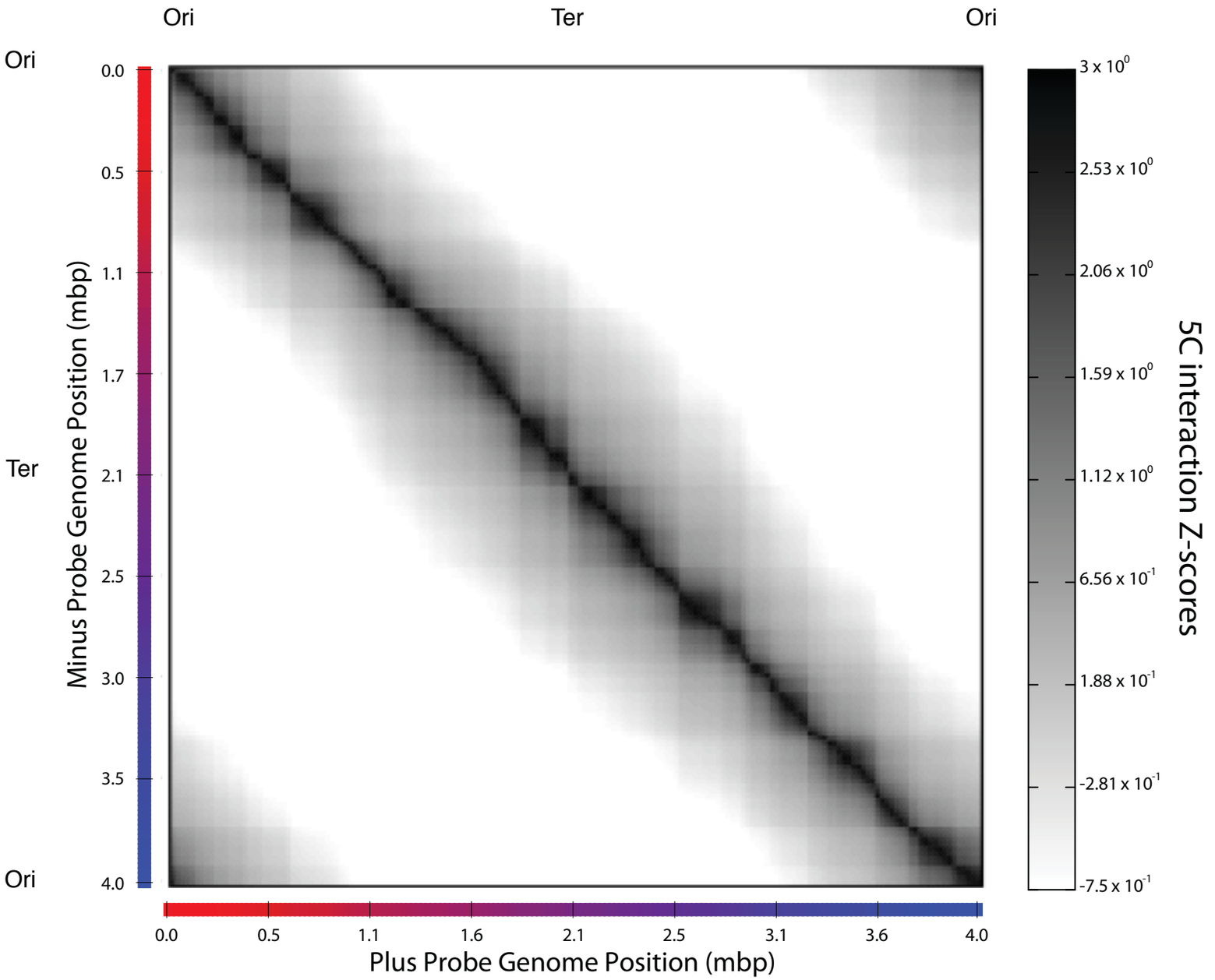
GM12878



K562

The genome of Caulobacter Crescentus

Toy interaction matrix



The genome of Caulobacter Crescentus

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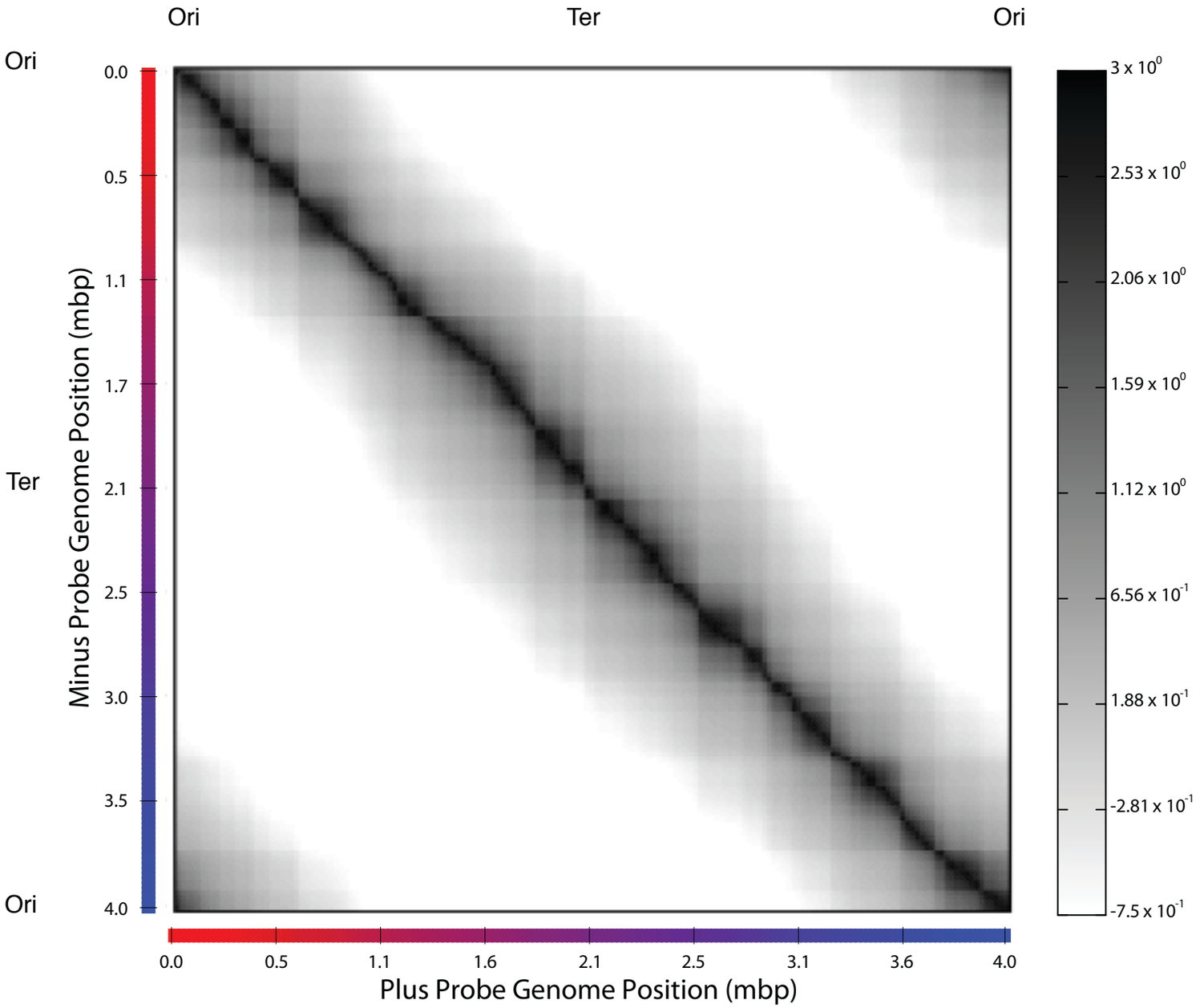
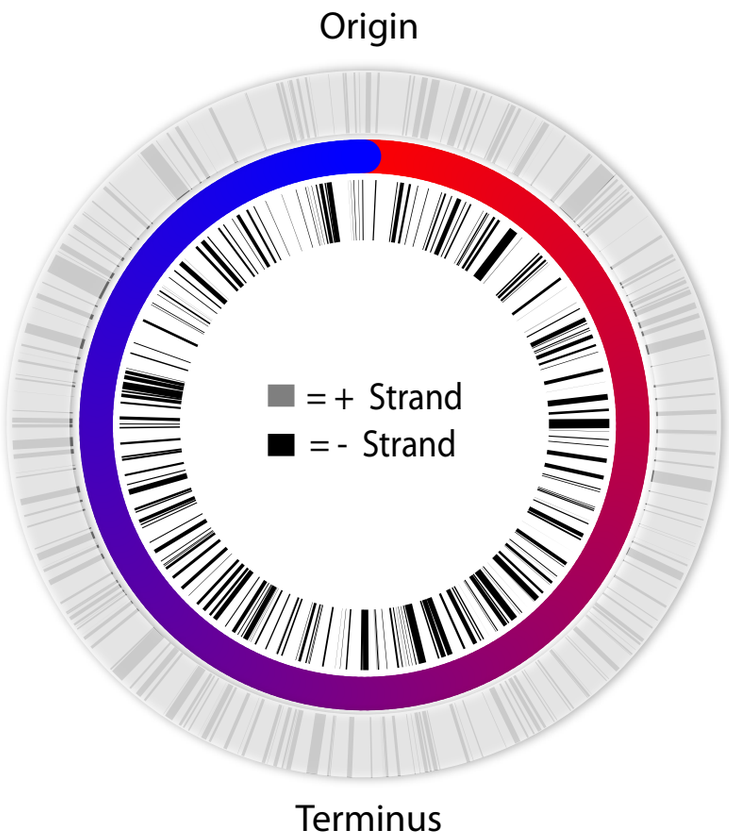
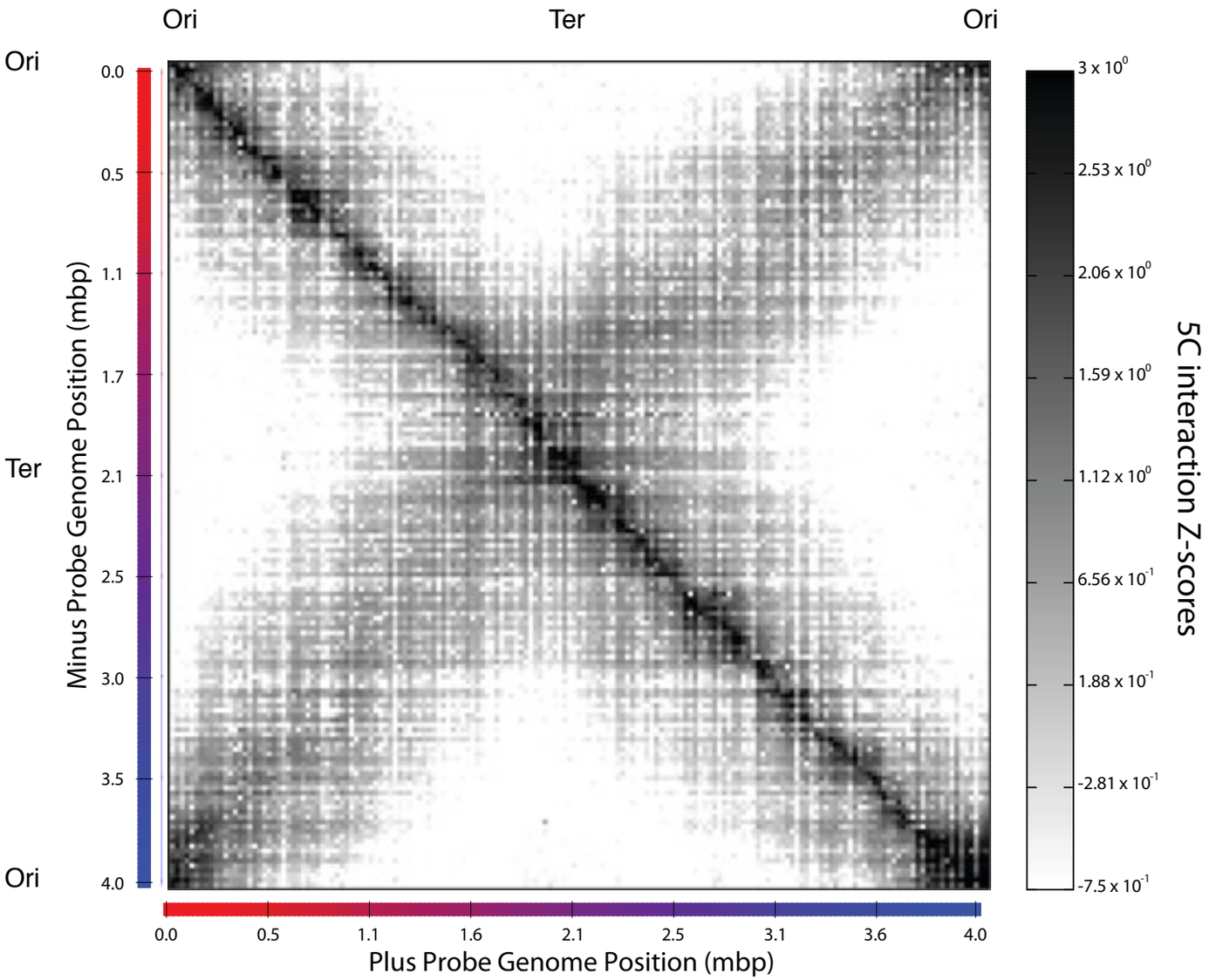




The genome of Caulobacter Crescentus

Real interaction matrix



The genome of Caulobacter Crescentus

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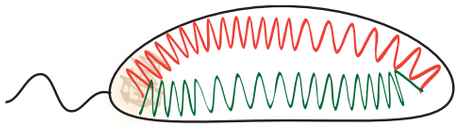
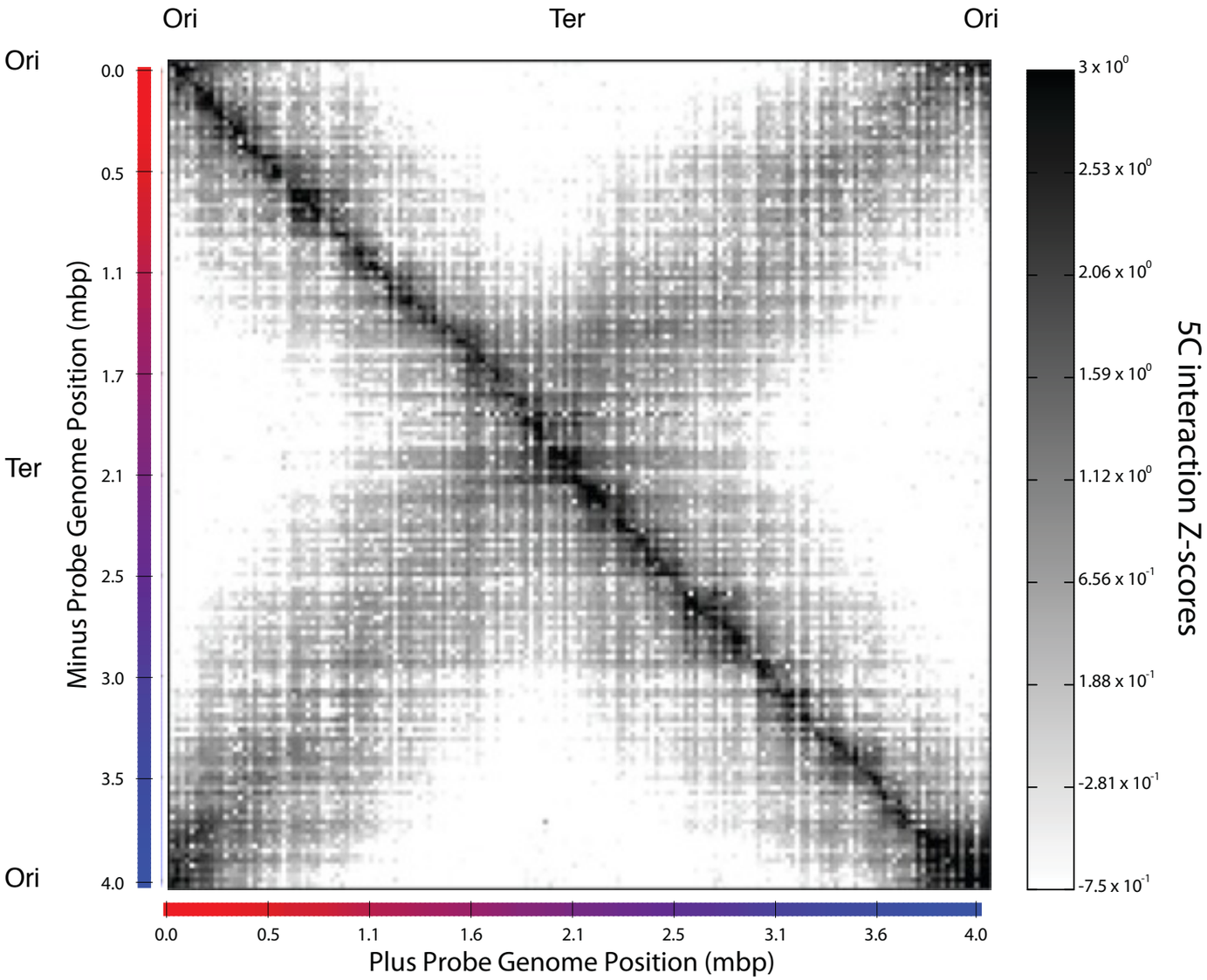
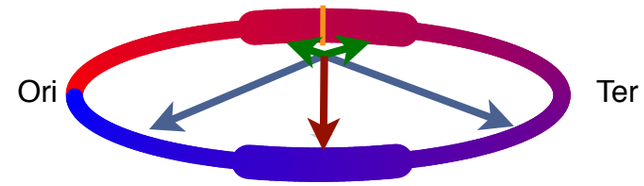
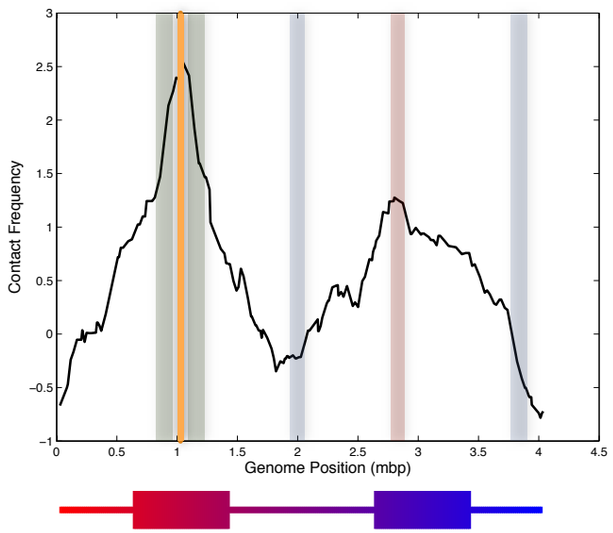








Take home message

Chromatin = DNA + (histone) proteins

The genome is well organized and hierarchically packaged

Histone modifications affect chromatin structure and activity

3C-like data measure the frequency of interaction between distant loci

How DNA is packaged

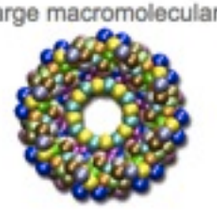
The Integrative Modeling Platform

http://integrativemodeling.org

home about news download doc wiki contact

IMP, the Integrative Modeling Platform

IMP's broad goal is to contribute to a comprehensive structural characterization of biomolecules ranging in size and complexity from small peptides to large macromolecular assemblies, by integrating data from diverse biochemical and biophysical experiments. IMP provides an open source C++ and Python toolbox for solving complex modeling problems, and a number of applications for tackling some common problems in a user-friendly way. IMP can also be used from the Chimera molecular modeling system, or via one of several web applications.



IMP is open source software, mostly available under the terms of the GNU Lesser General Public License (LGPL). (Some IMP modules are available under the GNU GPL instead.)

Get started with IMP by downloading it and checking out the documentation.

The IMP software is used as part of the National Center for Dynamic Interactome Research (NCDIR).

If you use IMP, please cite D. Russel, K. Lasker, B. Webb, D. Schneidman, J. Velázquez-Muriel, A. Sali, "Putting the pieces together: integrative structure determination of macromolecular assemblies", PLoS Biology, 2012. The main page of each IMP module in the documentation also lists publications relevant to that module.

cnag CRG

Installing IMP

Install the required libraries:

```
sudo apt-get install cmake
sudo apt-get install libboost1.49-all-dev
sudo apt-get install libhdf5-dev
sudo apt-get install swig
sudo apt-get install libcgal-dev
sudo apt-get install python-dev
```

Download the IMP tarball file from http://salilab.org/imp/ and uncompress it:

```
wget http://salilab.org/imp/get.php?pkg=2.0.1/download/imp-2.0.1.tar.gz -O imp-2.0.1.tar.gz
tar xzvf imp-2.0.1.tar.gz
```

Move to the IMP directory and compile the code

Compiling IMP

```
cd imp-2.0.1
cmake . -DCMAKE_BUILD_TYPE=Release -DIMP_MAX_CHECKS=NONE -DIMP_MAX_LOG=SILENT
make -j4
```

Once the compilation has finished, open the file setup_environment.sh in your IMP directory and copy the first lines into your ~/.bashrc file (if this file in not present in your home directory, create it). These lines should look like:

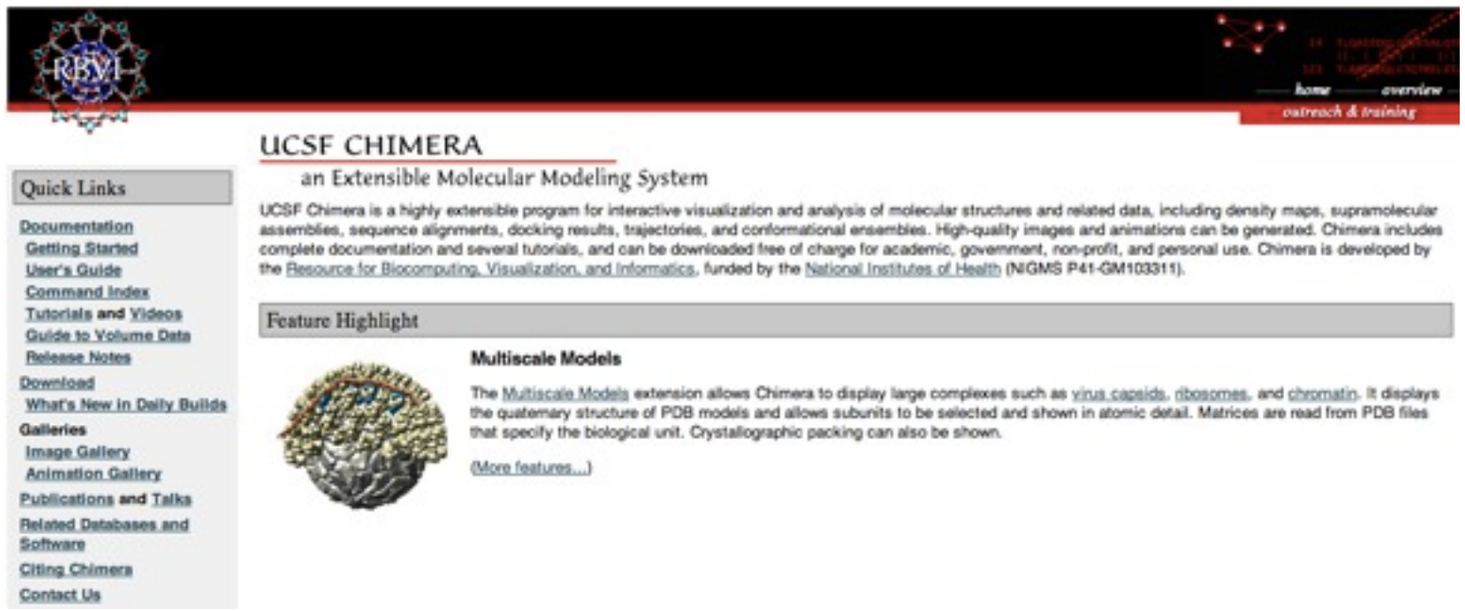
```
LD_LIBRARY_PATH="/SOMETHING/imp-2.0.1/lib:/SOMETHING/imp-2.0.1/lib:/SOMETHING/imp-2.0.1/src/
dependency/RMF/:$LD_LIBRARY_PATH"
export LD_LIBRARY_PATH

PYTHONPATH="/SOMETHING/imp-2.0.1/lib:/SOMETHING/imp-2.0.1/lib:/SOMETHING/imp-2.0.1/src/dependency/
RMF/:$PYTHONPATH"
export PYTHONPATH
```

>> Do not copy the lines above, copy them from setup_environment.sh,

where SOMETHING is replaced by your real path to IMP <<

Installing Chimera

http://www.cgl.ucsf.edu/chimera/



Chimera commands

Align
match.sh #1 #0

Select
select #model:particles

Measure
distance #0:1-2
angle #0:1-2

Display
vdwdefine #radius
shape tube #0 radius 1 bandLength 3 segmentSubdivisions 10
shape tube #0 rad 1 band 3 seg 10

Surface
molmap #all 80
color
transparency